## Remarks

The pending claims were rejected under § 112 first paragraph for scope of enablement and written description concerns. Claim 38 was rejected under § 112 second paragraph as missing essential process steps. Claim 48 was rejected under § 112 second paragraph for indefiniteness. Claims 1, 44, 45 and 46 were rejected under § 102 based on a Guijarro et al. article, WO 96/39129, or 5,858,326. In view of the amendment above, and remarks below, reconsideration is respectfully requested.

## § 112, First Paragraph Rejections

The Office Action has asserted that the application does not provide sufficient detail to enable the skilled person to understand and carry out the invention across the scope of the claims without undue experimentation, and that this deficiency reflects a failure in the written description so extensive as to call into question whether Applicant had possession of the claimed invention at the time of filing. It is respectfully submitted that those skilled in the art would find the specification sufficiently informative to broadly enable and to confirm that the Applicant possessed the concept at the time of filing.

Of course, the test in relation to enablement is not whether the application teaches the specific conditions required for every peptide falling within the scope of the claims, but whether the application provides sufficient teaching for a person of ordinary skill to carry out the invention without undue or unreasonable experimentation. The primary consideration in relation to written description is whether the specification shows by example or other content that the Applicant had possession of the invention at the time of filing.

The contribution of the present invention is the teaching that non-naturally occurring amyloid fibrils may be broadly

produced from peptides *in vitro*. Prior to this invention, it was believed that the ability to form amyloid fibrils was limited to peptides essentially based on proteins which form amyloid fibrils naturally *in vivo*.

The present application provided the first teaching that it was, in fact, possible to form amyloid fibrils from any peptide. Once this knowledge was provided by the present specification, with the examples of the specification, the invention was broadly taught to one of ordinary skill in the art. Once such a skilled person has read the present application, and the process conditions described therein, it is believed that he or she would be able to carry out the invention for a selected protein using only relatively minor tweaks to optimize for the particular protein.

Achieving some result would be straightforward. Achieving more optimal syntheses would require only routine and simple experiments.

In this regard, all the required methods to implement the discovery were well known in the art, and a variety of specific applications are exemplified in the present application. The experiments needed would consist mostly of optimization (e.g. tweaking the conditions in which the selected peptide is incubated and measuring how much amyloid fibril is formed).

For example, as taught in the application, the pH, temperature and peptide concentration can be optimized, and additional compounds such as alcohols can be added to further aid fibril formation. However, even without optimization, at least some enablement exists without significant tweaking.

The present application demonstrates the conditions and tests required for fibril formation from a number of specific proteins. The present application also provides guidance to the skilled reader in suggesting a number of factors that may be varied to achieve fibril formation.

For example, the application teaches the skilled reader to try tweaking the temperature, pH and peptide concentration of the experimental solution. The application goes on to teach a number of further changes that can be made, for example methods to denature the peptide. On the basis of these teachings, together with a background knowledge of other factors that can be varied or added, and the examples given, the skilled person could easily obtain suitable conditions for fibril formation from a selected peptide.

Crude aggregation and fibril formation should be <u>easily</u> achieved (and that is all that is required for enablement). If the Office Action is suggesting that optimization is required for enablement, that is not correct. In any event, once the basic enabling conditions exist it is straightforward to optimize the conditions. There would be no undue burden here, and no complex or arduous experiments would be required.

The point is that a key part of the invention is that a skilled person would have had no reason to try these straightforward experiments with these non-naturally occurring fibril goals. Once the specification provides that motivation, and examples, the implementation is straightforward.

In further support of these arguments, we file herewith a declaration by Professor Fred E. Cohen of the University of California, San Francisco. Professor Cohen has worked in the field of protein aggregation and fibril formation for many years. Professor Cohen's work in this field has focused on studying the mechanism by which prion proteins aggregate to form amyloid fibrils in various prion diseases. Professor Cohen was working actively in this field at the time the present invention was made. He therefore has a good knowledge of what a person of ordinary skill in this art would know and how that person would construe the content of the present application.

He both asserts that the specification is broadly enabling without undue experimentation to one skilled in the art, and that from the specification he believes that one skilled in the art would perceive that the inventor Dobson had possession of the invention as claimed. Hence, the § 112, first paragraph rejections should be withdrawn.

§ 112, Second Paragraph

The Office Action asserts that there are no decipherable steps in claim 38. However, claim 38 as now amended expressly recites steps so as to more clearly identify steps in the process. This objection is therefore believed to be overcome.

The other § 112 second paragraph rejection related to purported indefiniteness of claim 48. Without prejudice to claim scope, and solely for the purpose of facilitating prosecution, claim 48 has now been cancelled, to thereby render that rejection moot.

Art Rejections

All art rejections referred to claim 1. Claim 1 was previously canceled. In that claims 45-46 are all dependent on claim 38, Applicant suspects that the references to claim 1 were erroneous and that possibly a reference to claim 38 was instead intended. Hence, these art rejections will be responded to as if the rejections referred to claims 38 and 44-46.

A. Guijarro et al. (April 1998).

The present application has a U.S. effective filing date of March 30, 1999 (and of course a British priority date of September 21, 1998). The Guijarro et al. article was published in April of 1998. Thus, it was not published more than one year prior to the U.S. effective filing date. This is apparently recognized by the Office in view of the assertion of § 102(a) and not § 102(b).

However, § 102(a) requires that the work be by another. The named inventor of the present application is Christopher

M. Dobson. The named authors on the cited article were that same Christopher M. Dobson and four additional authors. As noted on that article, Mr. Dobson was the corresponding (and hence primary) main author of that article. Moreover, inventor Dobson has confirmed that those portions of the article pertinent to the claimed invention were derived from him.

While this is believed sufficient to remove the reference, if the Office wishes these statements by Mr. Dobson to be in a more formal form (e.g. a declaration), Applicant is prepared to submit such a declaration.

B. WO 96/39129 And U.S. 5,858,326.

Claim 38 is now amended to be directed to a process for preparing an amyloid fibril where there is the step of preparing a solution which is in a state so that nucleation and growth of a non-naturally occurring fibril can occur, and the step of allowing nucleation and growth of a non-naturally occurring fibril to take place. The present invention is thus directed to processes which result in the production of amyloid fibrils which do not occur naturally.

For example, the present invention would encompass the production of amyloid fibrils from artificially generated peptides, or from peptides which would not form such fibrils under *in vivo* conditions. The present invention explicitly does not encompass the natural formation of amyloid fibrils *in vivo*, or the formation of the same fibrils by other means, for example methods of forming *in vitro* the same fibrils which can be formed naturally *in vivo*.

This is clearly different from what is disclosed in WO 96/39129 or U.S. patent 5,858,326. These two documents are both directed to the aggregation of Aβ into amyloid fibrils. Aβ is well known to be capable of forming amyloid fibrils *in vivo*. This is believed to be the basis of Alzheimer's disease.

While these documents describe the formation of fibrils

by a synthetic method, the fibrils that are actually produced are naturally-occurring type amyloid fibrils. Both cited documents are directed to altering the rate of formation of such naturally-occurring fibrils. For example, U.S. patent 5,858,326 describes methods of increasing the deposition of Aβ amyloid fibrils in an animal model *in vivo*, and methods to screen for agents which are capable of decreasing the formation of such amyloid deposits from Aβ *in vivo*.

There is no teaching that the Aβ fibrils produced by the accelerating methods have been modified from those that would be formed naturally in, for example, Alzheimer's disease. Indeed, the basic purpose of these documents is to develop assays for compounds that may be useful in preventing or reducing the formation of Aβ amyloid deposits *in vivo* in Alzheimer's disease patients. Hence, the claims as amended clearly avoid anticipation.

Applicant particularly traverses any application of any "patentable weight" standard in the context of a § 102 anticipation rejection. An anticipation rejection requires that all claim elements be met. Limitations in steps cannot be ignored because the degree of difference is not perceived to be sufficient. That is an obviousness issue, not an anticipation issue.

Moreover, with regard to the obviousness issue, the enclosed declaration confirms that those skilled in the art would have found it surprising to form amyloid fibrils that are non-naturally occurring (e.g. paragraph 9 of the declaration).

Extension Petition

An extension petition is enclosed, together with a fee authorization. Hence, this amendment is timely since it is being filed on October 5, 2004 and extends the time for response for three months from July 5, 2004 through October 5, 2004.

## Conclusion

In view of the above amendment and remarks, and the enclosed submissions, reconsideration and allowance are respectfully requested with respect to amended claims 38-47, 49, 50 and 54-60. Apart from the three month extension fee authorized by the enclosed petition, no additional fees are believed to be needed for the consideration of this submission. However, if any are, please charge them to Deposit Account 17-0055.

Respectfully submitted,

Christopher M. Dobson

Dated: October 5, 2004 By: _____

Carl R. Schwartz, Esq.
Reg. No.: 29,437
Quarles & Brady LLP
411 East Wisconsin Avenue
Milwaukee, Wisconsin 53202
(414) 277-5715

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